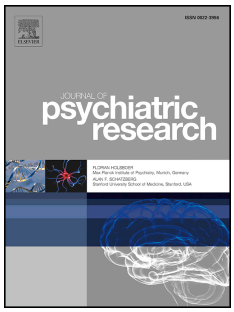
DOI:
10.1016/j.jpsychires.2016.11.002
10.1016/j.jpsychires.2016.11.002

Document Version
Peer reviewed version

Accepted Manuscript



An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders

Huai-Hai Wang, Min Cai, Hua-Ning Wang, Yun-Chun Chen, Rui-Guo Zhang, Ying Wang, Grainne M. McAlonan, Yuan-Han Bai, Wen-Jun Wu, Li Guo, Ya-Hong Zhang, Qing-Rong Tan, Zhang-Jin Zhang

PII: S0022-3956(16)30608-2

DOI: 10.1016/j.jpsychires.2016.11.002

Reference: PIAT 3001

To appear in: *Journal of Psychiatric Research*

Received Date: 20 June 2016

Revised Date: 23 October 2016

Accepted Date: 3 November 2016

Please cite this article as: Wang H-H, Cai M, Wang H-N, Chen Y-C, Zhang R-G, Wang Y, McAlonan GM, Bai Y-H, Wu W-J, Guo L, Zhang Y-H, Tan Q-R, Zhang Z-J, An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders, *Journal of Psychiatric Research* (2016), doi: 10.1016/j.jpsychires.2016.11.002.

JPR7272 (revised)

An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders

Huai-Hai Wang [a*], Min Cai [a*], Hua-Ning Wang [a], Yun-Chun Chen [a], Rui-Guo Zhang [a], Ying Wang [a], Grainne M. McAlonan [b], Yuan-Han Bai [a], Wen-Jun Wu [a], Li Guo [a], Ya-Hong Zhang [a], Qing-Rong Tan [a#], Zhang-Jin Zhang [c#]

[a] *Department of Psychiatry, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shaanxi 710021, China*

[b] *Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK*

[c] *School of Chinese Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China*

* Joint first authors

Correspondence should be addressed to either of the following authors:

Zhang-Jin Zhang, M.D., Ph.D.
School of Chinese Medicine
The University of Hong Kong
10 Sassoon Road, Pokfulam
Hong Kong, China
Tel: (+852)2589-0445
Fax: (+852)2872-5476
E-mail: zhangzj@hku.hk

Qing-Rong Tan, M.D.
Department of Psychiatry, Xijing Hospital
The Fourth Military Medical University
17 Changle Road,
Xi'an, Shaanxi 710032, China
Tel: (+86)-29-8477-5951
Fax: (+86)-29-8329-3951
E-mail: tanqingr@fmmu.edu.cn

Abstract

Background: Ziprasidone (ZIP) is often used with olanzapine (OLZ) in 'switch' and combination therapy but empirical evidence to support these strategies is limited. Objective: This study was therefore designed to compare the efficacy and tolerability of switching from OLZ to ZIP, the combination of both medications, and OLZ and ZIP monotherapy, in patients with schizophrenia spectrum disorders (SSD).

Methods: In this 12 week open-label, assessor-blinded randomized trial, 148 patients with SSD who had not used antipsychotics for at least 3 months were assigned to ZIP (n = 49) or OLZ monotherapy (n = 31); OLZ for 4 weeks then a switch to ZIP (OLZ/ZIP, n = 35); or combination therapy (OLZ+ZIP, n = 33). The severity of psychosis and abnormal involuntary movements was evaluated at baseline, 1, 2, 4, 8, and 12 weeks using standard instruments. Baseline-to-endpoint changes in weight gain and metabolic measures were compared.

Results: The efficacy of both OLZ/ZIP and OLZ+ZIP was comparable OLZ monotherapy and better than ZIP monotherapy in reducing overall psychotic and negative symptoms at most 8 and 12 week measurement points. Changes in weight gain, glucose, and lipid measures did not differ between OLZ/ZIP and OLZ+ZIP, but were markedly higher following OLZ monotherapy. The OLZ+ZIP group had the lowest overall incidence of adverse events and extrapyramidal symptoms of all the treatment regimens.

Conclusions: We conclude that combining ZIP and OLZ at the outset of treatment is superior to switching from OLZ to ZIP in terms of improving psychotic symptoms and limiting movement side effects without increasing the risk of metabolic syndrome.

Keywords: ziprasidone; olanzapine; switching therapy; Combination therapy; metabolic syndrome; schizophrenia spectrum disorders

1. Introduction

Although the availability of newer antipsychotic agents has greatly extended treatment options for psychotic disorders, it has failed to reduce the incidence of adverse drug reactions (Miyamoto et al., 2012). In contrast, atypical antipsychotics may even increase the risk of some adverse effects, in particular metabolic and movement disorders (Miyamoto et al., 2012). Optimizing antipsychotic treatment regimens through 'switch' and combination strategies may potentially achieve a balance between the therapeutic benefits and adverse effect risk, but direct evidence for these approaches is limited.

Olanzapine (OLZ) and ziprasidone (ZIP) are commonly used atypical agents with documented efficacy for the treatment of psychotic and manic disorders (Sikich, 2008), however, they have different therapeutic and side effect profiles (Mauri et al., 2014). In psychosis, OLZ treatment produces significantly greater symptom improvement, higher response rates and better completion rates compared to ZIP treatment (Breier et al., 2005; Grootens et al., 2011; Kinon et al., 2006; Simpson et al., 2004; Ou et al., 2013). OLZ therapy has also been reported to cause fewer extrapyramidal symptoms than ZIP (Breier et al., 2005). However, compared to ZIP, OLZ is associated with an increased risk of developing metabolic syndrome, manifesting as weight gain, dyslipidemia, glucose intolerance, and insulin resistance, leading to diabetes mellitus and cardiovascular disorders (Breier et al., 2005; Grootens et al., 2011; Kinon et al., 2006; Simpson et al., 2004; Ou et al., 2013). This has led to the proposition that combining these agents would improve efficacy and reduce adverse side effects of antipsychotic treatment.

Over the past decade, numerous studies have demonstrated that a switch to ZIP from other antipsychotic medications may limit the weight gain and other metabolic adverse

effects of treatment (Alptekin et al., 2009; Chen et al., 2012; Harvey et al., 2004; Lee et al., 2013; Rossi et al., 2008; Simpson et al., 2008; Weiden et al., 2003a,b). In contrast, there has been only one pilot trial of a combination therapy of ZIP and OLZ, and this did not find additional benefits of ZIP as an adjuvant in chronic schizophrenia (Henderson et al., 2009). To date, there are no published studies directly comparing the efficacy and tolerability of switch and combination therapy of ZIP and OLZ.

In the present study we tested the hypothesis that combining ZIP and OLZ would produce better treatment outcomes compared to switching from OLZ to ZIP in schizophrenia spectrum disorders (SSD). To achieve this, we compared efficacy measures and tolerability in terms of metabolic and motor disturbances in drug-free patients with SSD started on one of four treatment regimens: OLZ and ZIP monotherapy, switching from OLZ to ZIP, and the combination of OLZ and ZIP. We adopted an open-label, assessor-blinded randomized, parallel group design.

2. Materials and methods

2.1. Settings and participants

This open-label, assessor-blinded, randomized parallel group study was conducted in the Department of Psychiatry at Xijing Hospital of Fourth Military University in Xi'an of China between October 2012 and October 2015. The study protocol was approved by the Medical Ethical Committee of Xijing Hospital of the Fourth Military Medical University and registered in www.chictr.org (ChiCTR-OPC-15007529), a member of the WHO International Clinical Trial Registry Platform. All outcomes, measures, and sample size were identified prior to study initiation and did not undergo modification thereafter. A detailed and full explanation of the study goal, treatment procedures, and potential side effects was presented to each patient and/or his/her guardians by

psychiatrists. All participants and/or their guardians gave voluntary, written, informed consent for their acceptance of the study.

Inpatients who met the following criteria were eligible for participating in the study: (1) either gender aged 16-60 years; (2) had a diagnosis of SSD, including schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychotic disorder not otherwise specified according to the Classification of Mental and Behavior Disorders (10th version) (ICD-10) (World Health Organization, 1992); (3) the severity of participants' symptoms was at least moderate, as evidenced by the Positive and Negative Syndrome Scale (PANSS) total score of ≥70 (Kay et al., 1987); and (4) had no antipsychotic treatment for at least 3 months at study entry.

Subjects were excluded if they had: (1) serious comorbid cardiovascular, neurological, or other unstable medical conditions; (2) suicidal ideas or attempts or aggressive behavior; (3) laboratory tests of hepatic and renal function and/or electrocardiogram (ECG) beyond the normal reference ranges; (4) a history of alcoholism or drug abuse within the previous one year; (5) an investigational drug treatment within the previous 6 months; (6) pre-existing diabetes mellitus; or (7) pregnant and lactation.

2.2. Randomization and blinding

Participants were randomly allocated to 1 of 4 groups: ZIP and OLZ monotherapy, switching from OLZ to ZIP, and the combination of the two drugs in an approximate ratio of 1.5:1:1:1. For randomization, simple, complete, non-sequential random codes were produced in advance using a computer-generated block scheme.

The group allocation was done by the study coordinator (Y.H.B.) who was blind to participants' treatment condition. Clinical assessors, drug dispenses, data collector and

analysts were also blind to patients' medication status. Assessors and psychiatrists communicated with patients separately and were instructed not to acquire information about their other treatment conditions.

2.3. Treatment procedures

Orally administered OLZ dose in both mono- and combination therapy was initiated at 5 mg/day and escalated to an optimal dose within 2 weeks based on individual patients' response, with a maximum dose 20 mg/day. Orally administered ZIP in mono- and combination therapy was started at 80 mg/day and 40 mg/day, respectively, and titrated to a maximum of 160 mg/day within 2 weeks, depending on clinical and side effects. For switching therapy, OLZ was initiated at 5 mg/day; an optimal dose was achieved within 2 weeks and maintained to the end of 4 weeks. Tapering off OLZ was conducted from 5 weeks to 6 weeks. Over the same 2-week period, ZIP was given from an initial dose of 80 mg/day to a maximum of 160 mg/day. This switching regimen was designed based on our preliminary observation, which indicated that most patients' conditions were well controlled following 3-4 weeks of OLZ treatment with an optimal dose.

Concomitant use of other psychotropic drugs was generally not allowed. However, if clinically significant insomnia or extrapyramidal symptoms occurred that could potentially interfere with the continuation of experimental treatment, benzodiazepines (alprazolam or clonazepam), non-benzodiazepines (zolpidem or zopiclone), and anti-anticholinergic (trihexyphenidyl or injected scopolamine) agents were allowed only for acute use, without exceeding a cumulative duration of 14 days. Daily medications of each participant were monitored and recorded. Those who failed to maintain good medication compliance, defined as taking 80% or greater of the intended number of tablets, were removed from the study.

The prescription of medications was conducted by psychiatrists (W.H.H., H.N.W., Y.C.C., R.G.Z., and Q.R.T.) who were blind to clinical assessment results.

2.4. Clinical assessment

Clinical assessment was conducted at baseline, week 1, 2, 4, 8 and 12. Efficacy was measured using changes in scores on PANSS overall scales and subscales for positive, negative symptoms, and general psychopathology from the baseline to each time point. Safety and tolerability were assessed using the Treatment Emergent Symptom Scale (TESS) (Guy, 1976), with which all adverse events reported, elicited, or observed were recorded, including the date and time of onset, duration, severity, relationship with study drug, and action taken. The Extrapyramidal Symptom Rating Scale (ESRS) (Gharabawi et al., 2005) was used in addition to determine the incidence and severity of movement symptoms. Based on a maximum rating score on ESRS over the treatment period, the severity of extrapyramidal symptoms was categorized as none to mild (≤ 3), moderate (4 – 8), and severe (≥ 9) levels.

Clinical assessment was performed by assessors (M.C., Y. W., W.J.W., Y.H.Z., and L.G.) who were blind to patients' medication conditions. To ensure consistency of assessment, a training workshop was carried out before the recruitment started. An inter-rater reliability coefficient (κ value) of >0.80 on PANSS had been achieved from assessors involved in the study after the completion of training workshop. In most cases, all assessments of a subject from baseline to endpoint were conducted by the same assessor in order to minimize potential variations caused by different assessors.

2.5. Metabolic measurement

Body weight (kg), body mass index (BMI, kg/m^2), and blood pressure were measured daily. Fasting glucose, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured at baseline and endpoints. The ratio of TG to HDL (TG/HDL) was calculated as an additional parameter, as it is a

sensitive measure of insulin resistance (Brehm et al., 2004). All blood samples were collected after an overnight fast and analyzed by the same clinical laboratory. Net or percent changes in metabolic variables from baseline to endpoint were used in data analysis.

2.7. Statistical analysis

Based on a previous study in schizophrenia (Breier et al., 2005), compared to ZIP monotherapy, OLZ monotherapy should result in an additional approximately 8-point reduction in total PANSS score from baseline to 12 weeks, with an estimated standard deviation (SD) of 9. A sample size of 30 per group would therefore provide a greater than 90% power at significance level of 0.05.

A linear mixed-effect model was applied to compare overall PANSS and its subscale scores based on the intention-to-treat population, defined as participants who completed baseline and at least one evaluation after treatment. The model was established using time and group as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Age, sex and baseline total PANSS score were included as covariates. If differences in the slope among the 4 groups reached significance level, one-way analysis of variance (ANOVA) was used to further detect main effects, followed by Turkey test to detect between-group differences based on observed cases (OC), defined as the subset of subjects who had completed 12-week treatment and assessment per protocol. One-way ANOVA was also used to examine other continuous variables among the four groups. Categorical variables were analyzed using Chi-square (χ^2) test. Statistical significance was defined as a two-tailed $p < 0.05$. The analysis was conducted with SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Participant characteristics

Of 987 patients screened, 148 were recruited and randomly assigned to the four groups as shown in flowchart (Fig. 1); 111 (75.0%) of them completed the full course of treatment and assessment (Fig. 1). The mean (SD) age of the whole sample was 26.9 (± 6.4) years with the illness duration of 37.6 (±40.3) weeks, and the total PANSS score of 79.6 (±11.4) was indicative of moderate to severe illness. Ninety-two (62.2%) patients were experiencing their first episode of psychosis and others had relapsed. The overall PANSS scores of OLZ/ZIP and OLZ+ZIP groups were significantly lower than the other two groups (F = 6.255, df = 3,144, $p < 0.001$); other baseline variables were not statistically different among the four groups (Table 1). Overall medication compliance was approximately 98% across the four groups. No patients were removed from the study due to poor compliance rate (<80%). The discontinuation rate due to lack of efficacy or exacerbation of symptoms was 24.5% (12/49) in ZIP monotherapy, which was strikingly higher than the other three groups (0-3.0%, $\chi^2 = 91.309$, df = 3, $p < 0.001$) (Fig. 1).

The average doses of OLZ and ZIP given in the combination therapy were approximately 59% of the doses on monotherapy. The average OLZ dose on the switching therapy was 56.2% of the dose on OLZ monotherapy. The average ZIP doses were similar in the mono- and switching therapies (Table 2).

3.2. Efficacy

Changes from baseline in overall PANSS score and score on subscales are illustrated in Table 3 and Fig. 2. Linear mixed-effect model revealed significant differences in the slope among the four groups on total PANSS ($F_{3,880} = 21.261$, $p < 0.0001$), positive

($F_{3,880}$ = 24.830, p < 0.0001), negative symptoms ($F_{3,880}$ = 87.207, p < 0.0001), and general psychopathology ($F_{3,880}$ = 8.495, p < 0.0001). The four variables were significantly reduced over the course of treatment for each group (ZIP, $F_{5,247} \geq 24.116$, p < 0.001; OLZ, $F_{5,174} \geq 16.605$, p < 0.001; OLZ/ZIP, $F_{5,184} \geq 16.364$, p < 0.001; OLZ+ZIP, $F_{5,179} \geq 12.077$, p < 0.001). Treatment also produced a striking difference among the four groups in each variable (total PANSS, $F_{3,801}$ = 5.226, p = 0.0014; positive symptoms, $F_{3,801}$ = 9.298, p < 0.001; negative symptoms, $F_{3,801}$ = 21.550, p <0.001; general psychopathology, $F_{3,801}$ = 5.411, p = 0.0011). Between-group comparisons showed that the magnitude of reduction in PANSS total score and score on negative symptoms of the three OLZ-containing regimens was significantly greater than ZIP monotherapy at 8 and 12 weeks (adjusted p < 0.05), but not statistically significant between OLZ/ZIP and ZIP monotherapy at 12 weeks. OLZ/ZIP had a significantly greater improvement on negative symptoms than OLZ+ZIP at 1 week (adjusted p = 0.013). OLZ monotherapy produced a markedly greater reduction in score on positive symptoms compared to ZIP alone and OLZ/ZIP at 12 weeks (adjusted p < 0.05), but did not differ significantly from OLZ+ZIP. No significantly statistical group differences in the general psychopathology subscale were observed between any groups at any measurement points.

3.3. Weight and metabolic outcomes

Net or percent baseline-to-endpoint changes in weight and metabolic variables are shown in Table 4. The three ZIP-containing regimens did not differ in weight gain and BMI, or percent changes in glucose, cholesterol, and TG/HDL; but patients on OLZ monotherapy had a much greater increase in these variables than did patients on the three ZIP-containing regimens ($p \leq 0.043$).

3.4. Adverse events

Table 5 summarizes the incidence of adverse events that occurred in at least 5% of the patients in any treatment group. The proportion of patients with ESRS-measured extrapyramidal symptoms, their extrapyramidal symptom severity, and the proportion of patients who needed to use hypnotics/anxiolytics for insomnia and anticholinergic agents for extrapyramidal symptoms are also included in the Table. OLZ+ZIP group had a significantly lower incidence of any adverse events (24.2% vs. 65.3%-80.0%, χ^2 = 25.683, df = 3, $p < 0.001$), muscle rigidity (3.0% vs. 28.6-32.3%, $\chi^2 = 8.381$, df = 3, p = 0.039), and tremor (6.1% vs. 28.6%-36.7%, $\chi^2 = 9.926$, df = 3, $p = 0.019$) compared to the other three groups. The OLZ+ZIP group also had a significantly higher proportion of patients reporting 'none' and mild extrapyramidal symptoms (69.7% vs. 25.7%-48.4%) and much lower proportion with moderate (24.2% vs. 38.7%-57.1%) and severe symptoms (6.1% vs. 12.9%-18.4%) compared to the other three groups ($\chi^2 = 16.649$, p = 0.011). There were no group differences in the proportion of participants who needed to use concomitant medication for their insomnia ($\chi^2 = 1.198$, df = 3, $p = 0.754$) and/or extrapyramidal symptoms ($\chi^2 = 0.758$, df = 3, $p = 0.859$).

4. Discussion

This is the first study to directly compare the efficacy and tolerability of switching from OLZ to ZIP with the combination of both, and also with OLZ and ZIP monotherapy in patients with SSD. Consistent with prior studies (Breier et al., 2005; Grootens et al., 2011; Kinon et al., 2006; Simpson et al., 2004; Ou et al., 2013), the present study showed the superiority of OLZ over ZIP monotherapy in the control of psychotic episode of SSD. The OLZ-treated group had a greater reduction in total PANSS score and score on positive and negative subscales; whereas the ZIP-treated group had a higher discontinuation rate due to lack of efficacy or exacerbation of symptoms. Nevertheless, the three ZIP-containing regimens produced significantly less increase in

body weight, BMI, glucose, cholesterol, and TG/HDL ratio; so demonstrating advantages of ZIP over OLZ for metabolic adverse effects.

Furthermore, the efficacy of OLZ/ZIP and OLZ+ZIP was comparable to that of OLZ monotherapy. Both were more efficacious than ZIP monotherapy in reducing overall psychotic and negative symptoms, suggesting that switching and combination of the two drugs indeed can provide additional benefits. This was more apparent in OLZ+ZIP regimen. OLZ+ZIP had equivalent efficacy to OLZ alone in reducing overall psychotic and positive symptoms at 12 weeks, but OLZ/ZIP did not. OLZ/ZIP was inferior to OLZ alone in controlling positive symptoms at 12 weeks, although it achieved greater improvement on negative symptoms in the first week. While both OLZ/ZIP and OLZ+ZIP had similar effects in limiting weight gain and the increase of several metabolic parameters, patients on OLZ+ZIP exhibited much lower overall incidence of adverse events. OLZ+ZIP also caused the least extrapyramidal side effects. These results clearly indicate that combining ZIP and OLZ produces better treatment outcomes than switching from OLZ to ZIP in terms of reducing psychotic symptoms and adverse side effects, in particular movement disturbance.

Lower dosages of two antipsychotics have previously been suggested to cause fewer side effects than a high dosage of one antipsychotic (Kroken and Johnsen, 2012). In the present study, the average doses of both ZIP and OLZ used in OLZ+ZIP were only about 59% of those in monotherapy. Thus, the fewer adverse side effects observed in this study may, at least in part, be attributed to the lower dosages of the agents used. Similar results also have been observed in the combination of low-dosed clozapine and aripiprazole (Lim et al., 2004). It may also be possible that ZIP's action as a partial agonist at the 5HT1A receptor (Mauri et al., 2014) limits weight gain and food intake by

counteracting the 5-HT_{2C} antagonism which accompanies D_2 receptor blockade by both OLZ and/or ZIP (Kirk et al., 2004; Kroeze et al., 2003; Snigdha et al., 2008).

There are important differences between our study and previous studies of switching to ZIP. In those studies, the participants recruited were those who failed to achieve satisfactory response, had poor tolerability for metabolic side effects, or whose conditions had been stable under previous antipsychotic treatment (Alptekin et al., 2009; Chen et al., 2012; Harvey et al., 2004; Lee et al., 2013; Rossi et al., 2008; Simpson et al., 2008; Weiden et al., 2003). In contrast, the participants in the present study had not used antipsychotic medications for at least 3 months and the majority of them were first-episode subjects. This drug-free characteristic ensured that the results were not confounded by 'carryover effects' from previous antipsychotic treatment.

Several limitations of the current study should be considered. First, the sample recruited for the current study was a subset of relatively young adults with SSD with a relatively short illness duration, rather than chronic schizophrenia. This demographically "homogeneous" feature should be considered and we cannot say whether our results generalize to other cohorts, especially older individuals and/or those with chronic illness. Second, we did not conduct longer-term follow-up comparison of OLZ/ZIP and OLZ+ZIP in the maintenance treatment of SSD. Only limited data are available on the efficacy and tolerability of long-term treatment following switch to ZIP (Chen et al., 2012; Simpson et al., 2008), therefore the use of a combination of low-dose OLZ and ZIP for long-term maintenance treatment of schizophrenia deserves further investigation. Third, cardiovascular adverse effects were not formally evaluated in the present study. A large pharmaco-epidemiological study has shown a dose-dependent increase in the risk of sudden cardiac death (SCD) for patients treated with either classic or atypical antipsychotics, including OLZ (Ray et al., 2009). ZIP also has been found to be

associated with a high risk of QTc prolongation, which is an important predictor for torsade de pointes, ventricular fibrillation, and SCD (Strom et al., 2011). We postulate that lowering dosages of individual agents via combination regimens may be an effective strategy to reduce cardiovascular adverse effects, but this needs careful investigation. Finally, the baseline severity of psychotic symptoms varied significantly among the four groups. However, the use of baseline-to-endpoint changes and baseline total PANSS score as a covariate in the analysis of efficacy should help limit the impact of such baseline variations.

Collectively, the present study demonstrated that combining ZIP and OLZ is superior to switching from OLZ to ZIP in controlling psychotic symptoms and reducing movement side effects without increasing the risk of metabolic syndrome. The combination of low-dosed OLZ and ZIP could be considered as an option to replace an OLZ/ZIP switching therapy. We hope the present study will encourage further work to optimize antipsychotic polypharmacy regimens.

Role of funding source

This study was supported by Jiangsu Enhua Pharmaceutical Company (Q.R.T.), Establishment of Platform for Clinical Evaluation of New psychopharmacological Drugs (2012ZX09303014-002 for H.H.W.) from the Ministry of Science and Technology of China, and Natural Science Foundation of China (No.: 81571309 for H.N.W.).

Conflict of interest

All authors reported no conflicts of interest in this work.

Contributors

HHW, QRT, and ZZJ were involved in conception and design of the study, data analysis, and preparation of the manuscript. HNW, YCC, RGZ, YW, YHB, WJW, LG, and YHZ participated in patient recruitment, treatment, clinical assessment, and data collection. GMM provided critical comments on the paper. All authors have approved the final manuscript.

Acknowledgements

We thank Mr. Keith Wong for his assistance in statistical analysis.

References

Alptekin, K., Hafez, J., Brook, S., Akkaya, C., Tzebelikos, E., Ucok, A.E., Tallawy, H., Danaci, A.E., Lowe, W., Karayal, O.N., 2009. Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study. Int. Clin. Psychopharmacol. 24, 229-238.

Brehm, A., Pfeiler, G., Pacini, G., Vierhapper, H. & Roden, M., 2004. Relationship between serum lipoprotein ratios and insulin resistance in obesity. Clin. Chem. 50, 2316-2322.

Breier, A., Berg, P.H., Thakore, J.H., Naber, D., Gattaz, W.F., Cavazzoni, P., Walker, D.J., Roychowdhury, S.M., Kane, J.M., 2005. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. Am. J. Psychiatry 162, 1879-1887.

Chen, Y., Bobo, W.V., Watts, K., Jayathilake, K., Tang, T., Meltzer, H.Y., 2012. Comparative effectiveness of switching antipsychotic drug treatment to aripiprazole or ziprasidone for improving metabolic profile and atherogenic dyslipidemia: a 12-month, prospective, open-label study. J. Psychopharmacol. 26, 1201-1210.

Gharabawi, G.M., Bossie, C.A., Lasser, R.A., Turkoz, I., Rodriguez, S., Chouinard, G., 2005. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. Schizophr. Res. 77, 119-128.

Grootens, K.P., van Veelen, N.M., Peuskens, J., Sabbe, B.G., Thys, E., Buitelaar, J.K., Verkes, R.J., Kahn, R.S., 2011. Ziprasidone vs. olanzapine in recent onset schizophrenia and schizoaffective disorder: results of an 8-week double-blind randomized controlled trial. Schizophr. Bull. 37, 352-361.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology (revised). US Department of Health, Education, and Welfare, Bethesda, MD.

Harvey, P.D., Siu, C.O., Romano, S., 2004. Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Psychopharmacology (Berl) 172, 324-332.

Henderson, D.C., Fan, X., Copeland, P.M., Sharma, B., Borba, C.P., Forstbauer, S.I., Miley, K., Boxill, R., Freudenreich, O., Cather, C., Evins, A.E., Goff, D.C., 2009. Ziprasidone as an adjuvant for clozapine- or olanzapine-associated medical morbidity in chronic schizophrenia. Hum. Psychopharmacol. 24, 225-232.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kinon, B.J., Lipkovich, I., Edwards, S.B., Adams, D.H., Ascher-Svanum, H., Siris, S.G., 2006. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. J. Clin. Psychopharmacol. 26, 157-162.

Kirk, S., Neill, J.C., Jones, D.N., Reynolds, G.P., 2004. Ziprasidone suppresses olanzapine-induced increases in ingestive behaviour in the rat. Eur. J. Pharmacol. 505, 253–254.

Kroeze, W.K., Hufeisen, S.J., Popadak, B.A., Renock, S.M., Steinberg, S., Ernsberger, P., Jayathilake, K., Meltzer, H.Y., Roth, B,L., 2003. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 28, 519–526.

Kroken, R.A., Johnsen, E., 2012. Is rational antipsychotic polytherapy feasible? A selective review. Curr. Psychiatry Rep. 14, 244-251.

Lee, H.B., Yoon, B.H., Kwon, Y.J., Woo, Y.S., Lee, J.G., Kim, M.D., Bahk, W.M., 2013. The efficacy and safety of switching to ziprasidone from olanzapine in patients with bipolar I disorder: an 8-week, multicenter, open-label study. Clin. Drug Investig. 33, 743-753.

Lim, S., Pralea, C., Schnitt, J., Bowers, M.B., J.r., Cooper, C., 2004. Possible increased efficacy of low-dose clozapine when combined with aripiprazole. J. Clin. Psychiatry 65, 1284-1285.

Mauri, M.C. Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., Altamura, A.C., 2014. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 13, 1163-1191.

Miyamoto, S., Miyake, N., Jarskog, L.F., Fleischhacker, W.W., Lieberman, J.A., 2012. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol. Psychiatry 17, 1206-1227.

Ou, J.J., Xu, Y., Chen, H.H., Fan, X., Gao, K., Wang, J., Guo, X.F., Wu, R.R., Zhao, J.P., 2013. Comparison of metabolic effects of ziprasidone versus olanzapine treatment in patients with first-episode schizophrenia. Psychopharmacology (Berl) 225, 627-635.

Ray, W.A., Chung, C.P., Murray, K.T., Hall, K., Stein, C.M., 2009. Atypical antipsychotic drugs and the risk of sudden cardiac death. N. Engl. J. Med. 360, 225-235.

Rossi, A., Vita, A., Tiradritti, P., Romeo, F., 2008. Assessment of clinical and metabolic status, and subjective well-being, in schizophrenic patients switched from typical and atypical antipsychotics to ziprasidone. Int. Clin. Psychopharmacol. 23, 216-222.

Sikich, L., 2008. Efficacy of atypical antipsychotics in early-onset schizophrenia and other psychotic disorders. J. Clin. Psychiatry 69(Suppl 4), 21-25.

Simpson, G.M., Glick, I.D., Weiden, P.J., Romano, S.J., Siu, C.O., 2004. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am. J. Psychiatry 161, 1837-1847.

Simpson, G.M., O'Gorman, C.J., Loebel, A., Yang, R., 2008. Long-term improvement in efficacy and safety after switching to ziprasidone in stable outpatients with schizophrenia. CNS Spectr. 13, 898-905.

Snigdha, S., Thumbi, C., Reynolds, G.P., Neill, J.C., 2008. Ziprasidone and aripiprazole attenuate olanzapine-induced hyperphagia in rats. J. Psychopharmacol. 22, 567-571.

Strom, B.L., Eng, S.M., Faich, G., Reynolds, R.F., D'Agostino, R.B., Ruskin, J., Kane, J.M., 2011. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Am. J. Psychiatry 168, 193-201.

Weiden, P.J., Daniel, D.G., Simpson, G., Romano, S.J., 2003. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J. Clin. Psychopharmacol. 23, 595-600.

Weiden, P.J., Simpson, G.M., Potkin, S.G., O'Sullivan, R.L., 2003. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. J. Clin. Psychiatry 64, 580-588.

World Health Organization, 1992. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines.

Legends for figures

Fig. 1. Flowchart of screening and recruitment of study subjects with schizophrenia spectrum disorders (SSD). ZIP, ziprasidone; OLZ, olanzapine.

Fig. 2. Changes from baseline in score on overall Positive and Negative Syndrome Scale (PANSS) (A) and its subscales on positiv2 (B), Negative symptoms (C) and general psychopharmacology (D) in patients with schizophrenia spectrum disorders (SSD). Statistical analysis results are presented in Table 3. ZIP, ziprasidone; OLZ, olanzapine.

Table 1. Baseline characteristics of patients with SSD

Variables	ZIP (n = 49)	OLZ (n = 31)	OLZ/ZIP (n = 35)	OLZ+ZIP (n = 33)	All (n = 148)
Male, n (%) [a]	21 (42.9)	20 (64.5)	17 (48.6)	16 (48.5)	74 (50.0)
Age (year) [b]	26.3 ± 7.2	27.4 ± 7.0	27.0 ± 5.5	26.9 ± 5.2	26.9 ± 6.4
The illness duration (week) [b]	36.1 ± 48.5	39.4 ± 37.8	33.2 ± 36.9	42.9 ± 33.3	37.6 ± 40.3
Having family members with mental illnesses, n (%) [a]	7 (14.3)	5 (16.1)	6 (17.1)	6 (18.2)	24 (16.2)
First-episode subjects, n (%) [a]	30 (61.2)	17 (54.8)	27 (77.1)	18 (54.5)	92 (62.2)
Subtype of diagnosis, n (%) [a]					
Paranoid	38 (77.6)	23 (74.2)	28 (80.0)	25 (75.8)	114 (77.0)
Hebephrenic	8 (16.3)	6 (19.4)	5 (14.3)	7 (21.2)	26 (17.6)
Undifferentiated	3 (6.1)	2 (6.4)	2 (5.7)	1 (3.0)	8 (5.4)
Overall PANSS score [b]	84.4 ± 12.0	80.1 ± 12.2	77.4 ± 10.7*	74.4 ± 7.0*	79.6 ± 11.4
Body weight (kg) [b]	62.3 ± 11.5	62.5 ± 10.3	62.2 ± 10.9	62.1 ± 10.6	62.3 ± 10.8
BMI (kg/m^2) [b]	22.6 ± 3.8	22.2 ± 2.6	22.4 ± 2.4	22.0 ± 2.2	22.3 ± 3.0

[a] Categorical data were analyzed using Chi-square (χ^2) test. No statistically significant differences were observed among the four groups.

[b] Continuous data are expressed as mean ± SD and examined using one-way analysis of variance (ANOVA), * $p < 0.01$ compared to ZIP group.

SSD, schizophrenia spectrum disorders; ZIP, ziprasidone; OLZ, olanzapine; PANSS, the Positive and Negative Syndrome Scale; BMI, body mass index.

Table 2. Average doses of medications taken during the study [a]

	ZIP (n = 30)	OLZ (n = 27)	OLZ/ZIP (n = 27)	OLZ+ZIP (n = 27)	ANOVA *F*	*df*	*P*
OLZ (mg/day)	-----	16.9 ± 1.4	9.5 ± 1.0*	9.9 ± 4.2*	76.932	2,79	<0.001
ZIP (mg/day)	126.7 ± 18.5	-----	126.9 ± 15.3	74.8 ± 37.9*	45.819	2,82	<0.001

[a] Data are expressed as mean ± SD and examined using one-way analysis of variance (ANOVA), * $p < 0.001$ compared to monotherapy group. ZIP, ziprasidone; OLZ, olanzapine.

Table 3. Changes from baseline in score on overall PANSS and its subscales in patients with SSD [a]

Variables	ZIP (n = 49)	OLZ (n = 31)	OLZ/ZIP (n = 35)	OLZ+ZIP (n = 33)	Overall analysis	
					$F_{3,880}$	*P*
Overall					21.261	<0.0001
Week 1	-6.9 ± 9.1	-7.2 ± 11.4	-9.8 ± 7.8	-3.2 ± 14.2		
Week 2	-13.1 ± 8.3	-17.2 ± 15.5	-16.7 ± 7.5	-12.2 ± 15.5		
Week 4	-18.6 ± 8.1	-26.5 ± 14.8	-23.6 ± 8.4	-21.9 ± 17.0		
Week 8	-21.8 ± 8.8	-31.2 ± 16.2*	-28.2 ± 9.5*	-27.8 ± 13.3*		
Week 12	-25.1 ± 8.5	-34.7 ± 14.8*	-30.9 ± 10.4	-33.9 ± 11.7*		
Positive symptoms					24.830	<0.0001
Week 1	-2.3 ± 2.6	-2.5 ± 3.7	-2.7 ± 3.6	-1.6 ± 4.9		
Week 2	-4.3 ± 3.3	-5.3 ± 5.6	-4.8 ± 3.0	-4.0 ± 5.8		
Week 4	-6.2 ± 3.6	-8.7 ± 5.4	-6.4 ± 3.8	-7.0 ± 5.2		
Week 8	-7.4 ± 4.5	-9.7 ± 6.5	-7.3 ± 3.7	-8.1 ± 4.7		
Week 12	-7.3 ± 3.5#	-10.7 ± 6.2	-7.4 ± 3.8#	-9.0 ± 5.3		
Negative symptoms					87.207	<0.0001
Week 1	-0.9 ± 3.3	-2.1 ± 3.7	-3.2 ± 3.9^	-0.4 ± 5.4		
Week 2	-2.5 ± 4.0	-3.7 ± 5.9	-4.6 ± 4.3	-2.6 ± 5.3		
Week 4	-4.1 ± 3.7	-5.9 ± 3.9	-6.1 ± 4.8	-4.9 ± 5.2		
Week 8	-3.9 ± 3.4	-7.0 ± 4.2*	-7.3 ± 4.9*	-6.7 ± 5.0*		
Week 12	-5.1 ± 3.0	-8.7 ± 3.9*	-7.7 ± 4.8*	-9.4 ± 4.7*		
General psychopathology					8.495	<0.0001
Week 1	-3.8 ± 6.5	-2.5 ± 8.0	-3.9 ± 3.3	-1.3 ± 7.6		
Week 2	-6.3 ± 5.0	-8.2 ± 10.3	-7.3 ± 3.2	-5.5 ± 7.5		
Week 4	-8.3 ± 5.4	-11.9 ± 9.5	-11.1 ± 3.7	-10.0 ± 8.4		
Week 8	-10.4 ± 5.5	-14.5 ± 9.5	-13.6 ± 4.9	-13.1 ± 6.3		
Week 12	-12.7 ± 5.3	-15.3 ± 9.4	-15.8 ± 5.9	-15.5 ± 7.7		

[a] Data are expressed as mean ± SD. Overall statistical significance was analyzed using a linear mixed-effect model analysis. Between-group differences were further evaluated using one-way analysis of variance (ANOVA). * $p < 0.05$ compared to ZIP group; # $p < 0.05$ compared to OLZ group; ^ $p = 0.013$ compared to OLZ/ZIP group. PANSS, the Positive and Negative Syndrome Scale; SSD, schizophrenia spectrum disorders; ZIP, ziprasidone; OLZ, olanzapine.

Table 4. Baseline-to-endpoint changes in weight gain and metabolic variables in patients with SSD [a]

Variables	ZIP (n = 30)	OLZ (n = 27)	OLZ/ZIP (n = 27)	OLZ+ZIP (n = 27)	ANOVA	
					$F_{3,108}$	*P*
Net weight gain (kg)	-0.1 ± 2.3*	3.9 ± 2.6	0.0 ± 1.7*	0.8 ± 1.8*	20.575	<0.001
Net change in BMI (kg/m^2)	0.0 ± 0.8*	1.4 ± 1.0	0.0 ± 0.6*	0.3 ± 0.6*	19.272	<0.001
Glucose (%)	6.3 ± 13.0*	19.2 ± 19.7	8.3 ± 10.8*	9.7 ± 20.0*	3.307	0.023
TG (%)	42.2 ± 138.4	66.9 ± 83.8	26.2 ± 59.8	32.1 ± 62.1	1.027	0.384
Cholesterol (%)	-5.8 ± 25.5*	20.0 ± 30.8	-0.5 ± 26.2*	1.0 ± 27.5*	4.551	0.005
HDL (%)	5.6 ± 35.4	-20.4 ± 34.3	10.0 ± 72.4	-6.6 ± 29.4	2.364	0.075
LDL (%)	14.4 ± 50.2	32.6 ± 62.7	11.8 ± 50.9	31.4 ± 74.3	0.908	0.440
TG/HDL (%)	49.7 ± 142.0*	157.8 ± 201.7	44.5 ± 97.2*	60.4 ± 94.5*	3.907	0.011

[a] Data are expressed as mean ± SD and evaluated using one-way analysis of variance (ANOVA), followed by Student-Newman-Keuls method. * $p \leq 0.043$ compared to OLZ group. SSD, schizophrenia spectrum disorders; ZIP, ziprasidone; OLZ, olanzapine; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 5. The incidence of major adverse events occurred in patients with SSD, the proportion with different severity of ESRS-measured extrapyramidal symptoms and the proportion required to use hypnotics/anxiolytics for insomnia and anticholinergic agents for extrapyramidal symptoms, n (%) [a]

Adverse event	ZIP (n = 49)	OLZ (n = 31)	OLZ/ZIP (n = 35)	OLZ+ZIP (n = 33)	χ^2 value	*p* value
Any	32 (65.3)	22 (71.0)	28 (80.0)	8 (24.2)	25.683	<0.001
Dizziness	7 (14.3)	2 (6.5)	3 (8.6)	0	5.546	0.136
Muscle rigidity	15 (30.6)	10 (32.3)	10 (28.6)	1 (3.0)	8.381	0.039
Tremor	18 (36.7)	9 (29.0)	10 (28.6)	2 (6.1)	9.926	0.019
Akathisia	8 (16.3)	3 (9.7)	7 (20.0)	2 (6.1)	3.550	0.314
Nausea/vomiting	6 (12.2)	2 (6.5)	4 (11.4)	1 (3.0)	2.612	0.455
Constipation	9 (18.4)	4 (12.9)	8 (22.9)	3 (9.1)	2.787	0.426
Insomnia	15 (30.6)	6 (19.4)	13 (37.1)	4 (12.1)	6.864	0.076
Dry mouth	6 (12.2)	4 (12.9)	3 (8.6)	2 (6.1)	1.196	0.754
ESRS					16.649	0.011
None to mild	16 (32.6)	15 (48.4)	9 (25.7)	23 (69.7)		
Moderate	24 (49.0)	12 (38.7)	20 (57.1)	8 (24.2)		
Severe	9 (18.4)	4 (12.9)	6 (17.2)	2 (6.1)		
The use of medication to treat side effects						
Hypnotics/ anxiolytics	11 (22.4)	7 (22.6)	9 (25.7)	5 (15.2)	1.198	0.754
Anticholinergic	13 (26.5)	9 (29.0)	12 (34.3)	11 (33.3)	0.758	0.859

[a] Data were analyzed using Chi-square (χ^2) test (df = 3). SSD, schizophrenia spectrum disorders; ZIP, ziprasidone; OLZ, olanzapine; ESRS, extrapyramidal symptom rating scale.

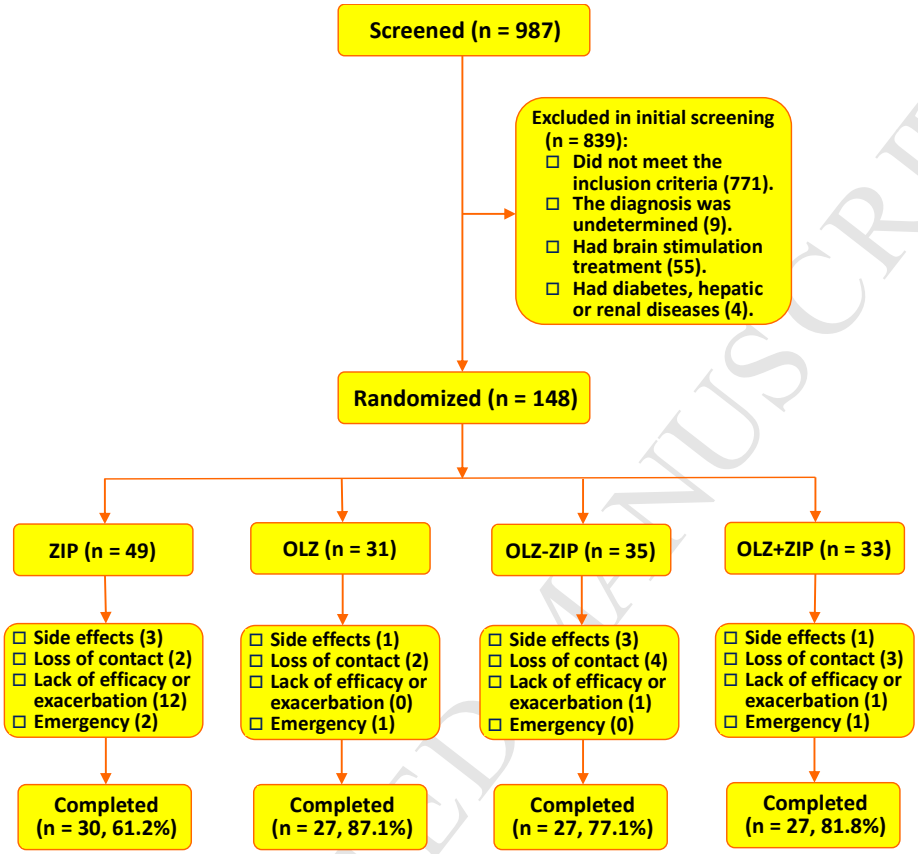


Fig. 1

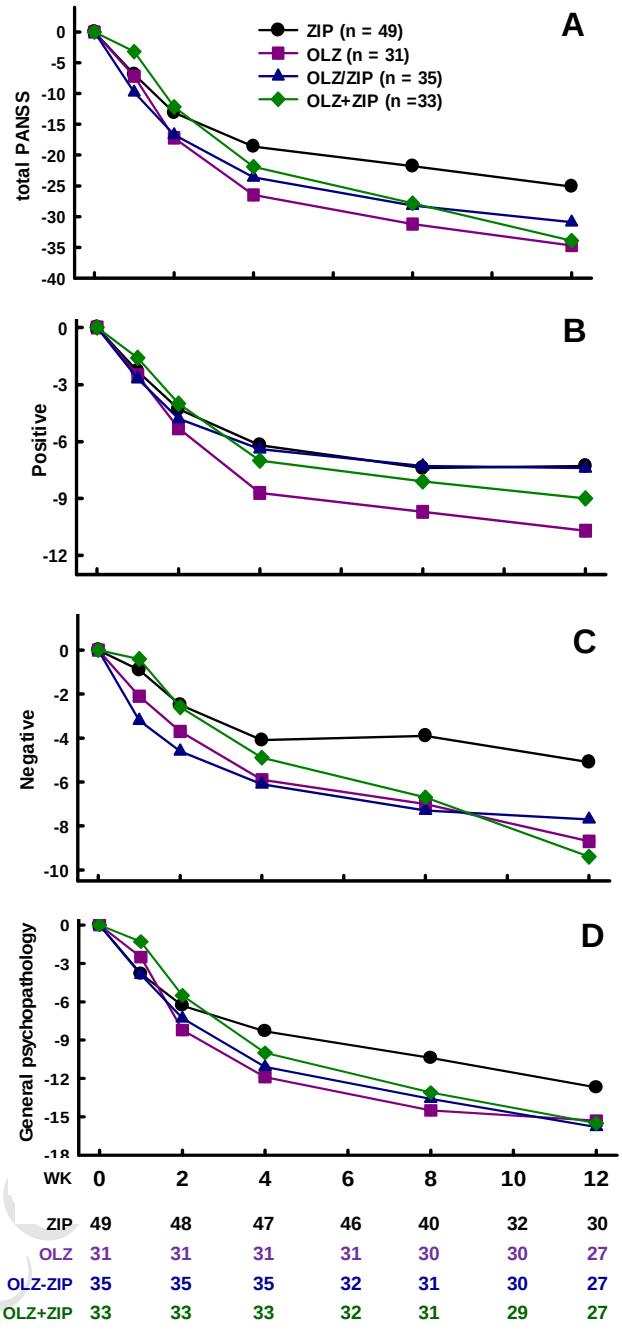

A
ZIP (n = 49)
OLZ (n = 31)
OLZ/ZIP (n = 35)
OLZ+ZIP (n =33)
total PANSS
0
-5
-10
-15
-20
-25
-30
-35
-40
B
Positive
0
-3
-6
-9
-12
C
Negative
0
-2
-4
-6
-8
-10
D
General psychopathology
0
-3
-6
-9
-12
-15
-18
WK 0 2 4 6 8 10 12
ZIP 49 48 47 46 40 32 30
OLZ 31 31 31 31 30 30 27
OLZ-ZIP 35 35 35 32 31 30 27
OLZ+ZIP 33 33 33 32 31 29 27

Fig. 2

Acknowledgements

We thank Mr. Keith Wong for his assistance in statistical analysis.

Contributors

HHW, QRT, and ZZJ were involved in conception and design of the study, data analysis, and preparation of the manuscript. HNW, YCC, RGZ, YW, YHB, WJW, LG, and YHZ participated in patient recruitment, treatment, clinical assessment, and data collection. GMM provided critical comments on the paper. All authors have approved the final manuscript.

Role of funding source

This study was supported by Jiangsu Enhua Pharmaceutical Company (Q.R.T.), Establishment of Platform for Clinical Evaluation of New psychopharmacological Drugs (2012ZX09303014-002 for H.H.W.) from the Ministry of Science and Technology of China, and Natural Science Foundation of China (No.: 81571309 for H.N.W.).